

A. A. BERTHOLD AND THE FIRST ENDOCRINE EXPERIMENT: SOME SPECULATION AS TO ITS ORIGIN *

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There were thirty-nine contributions in the volume for 1849 of Dr. Johannes Müller's *Archiv für Anatomie, Physiologie und wissenschaftliche Medicin* (1). No doubt Dr. Müller, like any editor, permitted himself a few moments of satisfaction and relaxation when the printers had finished their task and the completed volume lay on his desk. As he turned the pages in final inspection, what was his opinion, one wonders, of the third article, by "Prof. Berthold in Göttingen"? This was a short paper, concise and matter of fact, on the transplantation of testes.¹ That Prof. Berthold's report received more than brief attention from Dr. Müller or any one else is unlikely; it seems not to have been mentioned in print for the next sixty years (3). But the observations which the German physiologist set forth established a new science.

Arnold Adolf Berthold (1803-1861), physician and investigator (he also discovered, with Bunsen, the use of a preparation of hydrated oxides of iron as an antidote for arsenic poisoning (4)), relates in his little paper (1) how he caponized six young cockerels, then returned single testes to the body cavities of some of the birds. The grafts, placed among the intestines, became vascularized. Berthold observed that the host birds continued to exhibit the sexual behavior and accessories of normal young roosters. At autopsy he found that the nerve supply of the grafted testes had not been re-established. Berthold concludes:

Da nun aber an fremde Stellen transplantierte Hoden mit ihren ursprünglichen Nerven nicht mehr in Verbindung stehen können, und da es, wie aus dem dritten Satze einleuchtet, keine specifischen, der Secretion vorstehenden Nerven giebt, so folgt, dass der fragliche Consensus durch das productive Verhältniss der Hoden, d. h. durch deren Einwirkung des Blutes auf den allgemeinen Organismus überhaupt, wovon allerdings das Nervensystem einen sehr wesentlichen Theil ausmacht, bedingt wird (1, pages 45-46).

In other words, since maintenance of sexual behavior and appearance

* Read before the Beaumont Club, Yale University, on 13 May 1949.

¹ D. P. Quiring has made an English translation (2) of the obscure Berthold paper.

could not have been accomplished by the nerves, which were severed, the results must have been due to a contribution of the testes to the blood and then to the action of the added substance throughout the entire body. (The term *hormone* was to be coined later by William B. Hardy (3, page 2)). Here, in a magnificent experiment, was the first proof of endocrine function as we now understand it.

While Berthold's demonstration is clear enough, an important and related question appears to have been left unanswered. *Why* did he do the experiment? What line of reasoning led him to devise this research? We must remember that before 1849 endocrinology as such did not exist. It is true that a realization of the results of castration had come down from antiquity, but without actual explanation. John Hunter had shown by 1771 that transplantation of rooster testes to hens was feasible (5), but the writer has found no indication that Berthold was aware of Hunter's work. It is difficult to believe that intuition or whim alone could have been responsible for a crucial experiment. What, then, was the origin of his hypothesis?

Berthold has not, to the writer's knowledge, left a direct answer to this question; therefore, perhaps we are entitled to a guess or two. His list of publications includes three editions (6, 7, 8) of a textbook of physiology. All three editions were published before his classic paper, and they give us some clues. For the sake of background, the theory of pangenesis, inherited in its elements from the Greeks, requires mention. According to the theory, each part of the body of a prospective parent contributes a particle or molecule for assembly, in the reproductive tract, into an aggregate capable of producing a miniature offspring resembling the parent. This idea, an interesting predecessor, in a sense, of the modern concept of chromosomes and genes, was re-interpreted by several naturalists, among them Maupertuis, Buffon, and Darwin (9).

Each of the three editions of Berthold's textbook contains roughly the same passage presenting his theory of inheritance. Translated, the 1848 edition states (8, pages 568-569):

Up to a certain time in the development of the individual, the sex organs conduct themselves as ordinary structures belonging to the organism, but when the individual is sufficiently developed, the organs begin their sexual activity. They do not create a new being, but the individual organism serves itself as their intermediary in the production of the new being. The mediating organs [*in the 1829 edition, the organs responsible for the animal's ability to reproduce*] are secretors or glands; what they form, they produce like other glands, from the general humoral aggregate, from the blood. But just as the glands produce not genuine educts [*i. e., substances separated unchanged from the blood*] but products [*i. e., new substances*], so also



the material for generation does not exist as such in the blood; rather, it is only prepared therefrom. This is a concept completely at variance with the theory of Buffon that each organ produces a miniature likeness which subsequently is deposited in the sex organ; if it does not reach its destination, it sometimes gives rise to an intestinal worm.

Berthold goes on to emphasize that the sex organs are significant only as intermediaries in the perpetuation of the species. But, he continues,

. . . in order to be able to function for the entire organism they [the gonads] must have formed and developed themselves in connection with the entire organism and its systems and organs. . . . This relation . . . is mediated chiefly through two processes, namely, through the nervous and vegetative systems. The nervous system is above all the regulator of the functions of the animal organism, and from the blood proceeds all formation and secretion, including the [secretion] of the material for procreation. Certain it is that from the blood by means of the action of the testes and ovaries the seminal and egg fluid is produced from which the sperm and egg cells are formed; that these fluids can be extracted from the blood may be explained [by assuming] that each organ through which the blood flows acts according to its particular nature upon it [the blood] and modifies it according to its particular nature. Such a quality of the blood, wherein the organism as a whole is represented with its characteristics comprises, in relation to the characteristic vital manifestations of the sex organs, the special reason for the formation of the material for reproduction. . . .

More briefly, Berthold's idea is about as follows. Each organ of the body makes a specific and characteristic contribution to the blood; the various contributions are pooled in the blood and brought to the gonads. The latter, acting as intermediaries, remove the various substances from the blood and manufacture from them new substances, sperm and ova; these germ cells carry within them the potentiality for forming new structures like those of the parents.²

Berthold agrees with Buffon's idea that each part of the body contributes specifically and characteristically to the blood stream; as a matter of fact, we still hold to this theory as far as the endocrine organs are concerned, although we do not accept the principle of Berthold's corollary

² The general hypothesis that numerous parts of the body contribute to the blood stream had been set forth in 1775 by Théophile de Bordeu in his *Analyse médicale du sang*: ". . . chacun (des organes) aussi sert de foyer et de laboratoire à une humeur particulière qu'il renvoie dans le sang après l'avoir préparée dans son sein, après lui avoir donné son caractère radical" (quoted by Neuburger, M.: Théophile de Bordeu (1722-1776) als Vorläufer der Lehre von der inneren Sekretion. *Wien. klin. Wschr.*, 11, 1367-1368, 1911) and in 1801 by J. J. C. Legallois (3). There is no record that either Bordeu or Legallois put the hypothesis to experimental test, nor does Berthold indicate whether his own hypothesis was to any extent derived from those of the earlier writers. \$8.50.

(*e. g.*, that insulin is responsible for the formation of the fetal pancreas). But Berthold adds the apparently new idea that the gonads, receiving *aus der allgemeinen Säftemasse, aus dem Blute* the special contributions from every area of the organism, then proceed to manufacture from these contributions something new, the ova and sperm. (Again, actually, this is partly true, since the gonads cannot survive and maintain gametogenesis unless nourished by numerous materials supplied by the blood, but this is not what Berthold meant.) Thus the investigator had two useful ideas at his disposal: organs make specific contributions to the blood stream, and the latter carries the contributions to a special site where they are utilized for a particular purpose.

Thus far we can be reasonably sure of our ground, but hereafter we must speculate. It seems likely that Berthold, familiar with such phenomena as puberty and the results of castration, realized that some hypothesis must be devised to explain the control of the gonads over the sex characters and sexual behavior. In his textbook he had mentioned only the germ cells as products of the gonads, and he had not suggested that the germ cells could function as blood borne regulators of sexual development and function. But if the idea came to him that the testis, like other parts of the body (according to his theory), might, in addition, release a specific product into the blood and that this product might have definite effects on the accessory sex structures, then his hypothesis would have been complete.

It is evident from his paper that there was an alternative hypothesis. The ability of the nervous system to control and integrate many of the activities of the body was well appreciated. The reproductive system is richly supplied with nerves. What part might be played by the latter?

The two hypotheses were now ready for test; if Berthold had thought of a third possible explanation, he does not mention it. A crucial experiment was devised and performed; the results were clear cut, the fact was demonstrated, and the answer was unequivocal. No investigator asks for more.

Why the ingenious physiologist appears to have gone no further with his discovery is not known. He lived for twelve years after publication of his results. Perhaps he lost interest, or perhaps his experiment was ridiculed, or perhaps he did not appreciate that he had clearly marked a path into a new field of science.

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